Factors Associated with Biochemical Remission after Microscopic Transsphenoidal Surgery for Acromegaly

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J Neurol Surg B 2014;75:47–52.

Abstract

Objectives To analyze surgical outcomes and predictive factors of disease remission in acromegaly patients who underwent microscopic transsphenoidal surgery (TSS) for a growth hormone (GH)-secreting adenoma.

Design A 6-year retrospective review of 86 consecutive acromegaly surgeries.

Setting Procedures performed at a single institution by a single surgeon.

Participants Seventy acromegaly patients.

Main Outcome Measures Demographic information, preoperative laboratory values, tumor imaging data, and morphological and immunohistochemical data were collected. Predictive values using the latest and most stringent biochemical remission criteria were determined using univariate and multivariate statistical analyses.

Results Remission rate for 59 (18 males) acromegaly patients meeting the study inclusion criteria was 52.5%. Remission rates for micro- and macroadenomas were 81.8% and 45.8%, respectively. Patients of older age, with a smaller tumor, lower Knosp grade, lower preoperative GH, and insulinlike growth factor 1 levels were more likely to achieve remission. Remission rate decreased significantly with repeat surgeries. Those patients with adenomas that stained positive for somatostatin receptor subtype 2A were less likely to experience tumor recurrence and more likely to respond to medical treatment with persistent or elevated GH hypersecretion.

Conclusions Microscopic TSS continues to be a viable means for treating acromegaly patients. Patients should be followed long term.

Keywords
- acromegaly
- remission
- transsphenoidal surgery

Introduction

Acromegaly is a disorder characterized by excessive growth hormone (GH) secretion, which, in most cases, is caused by a GH-secreting pituitary adenoma. An excess of GH can lead to significant morbidity largely because of the development of cardiovascular disease, musculoskeletal deformity, and

received
April 8, 2013
accepted after revision
June 27, 2013
published online
September 9, 2013

DOI http://dx.doi.org/10.1055/s-0033-1354578.
ISSN 2193-6331.

diabetes mellitus.[1–5] Surgical removal of the tumor via a transsphenoidal (TSS) approach is the first choice of treatment offered to patients. Reportedly, only 50 to 70% of cases attain remission after an initial resection even in the hands of the most experienced pituitary surgeons.[6–17] Therefore, close monitoring of cure/remission postoperatively is paramount to recommendations regarding adjuvant therapy, when appropriate.

Over the years, criteria determining remission have become more stringent.[18,19] New consensus guidelines recommend normal (age/sex-adjusted) insulinlike growth factor (IGF)-1, GH random (GHr) (fasting or nonfasting) <1 mg/L, and a GH nadir (GHn) during an oral glucose tolerance test (OGTT) <0.4 mg/L.[20] In a significant number of cases, adjuvant medical treatment is required postsurgery. Medical therapy includes somatostatin receptor ligands (SRLs), GH receptor antagonists, and dopamine agonists.[21] It has been reported that some histologic and immunochemical characteristics are predictive of tumor response to medical therapies.[22–26] The predictive value of these characteristics for responsiveness to surgical treatment has not been studied. In this retrospective study, we reviewed outcomes after TSS in acromegalic patients at our center between January 2006 and December 2011. We also analyzed factors associated with remission after surgery including the histologic and immunochemical patterns of tumor cells to determine predictive factors of remission.

Methods

Patients

From January 2006 to December 2011, 70 patients (86 surgical cases) with GH-secreting pituitary adenomas were operated on via a TSS approach at a single institution (Oregon Health & Science University) by a single neurosurgeon. All patients were diagnosed as having GH-secreting pituitary adenomas with positive results on an OGTT and sellar dynamic magnetic resonance (MR) imaging. Patients who had undergone preoperative medical treatment, including with SRLs were excluded, and a final 59 patients were included in the analysis. Therefore, in this article, analysis specifically measures the remission rate of acromegaly patients' response to the surgical treatment. An analysis of the same group of patients that measured response to medical treatment was previously published.[22] This retrospective study was approved by the Oregon Health & Science University institutional review board.

Surgical Procedure

A conventional TSS approach with an operating microscope (Leica, Switzerland) and a Polestar N-10 (0.12T) intraoperative MR (Odin Medical Technologies, Newton, MA) scanner was used. Surgical approach varied according to tumor location and size, and any evidence of cavernous sinus or suprasellar space invasion. As confirmed by preoperative MR images, intrasellar tumors were completely removed in all cases. If there was evidence of cavernous sinus invasion, every effort was made to achieve total resection. Pseudocapsules were completely removed because they can be a major source of tumor recurrence.[27] If there was any suspicion of dural invasion, all exposed dura mater was removed as much as was possible. Immediately postsurgery, intraoperative MR imaging was used to confirm the extent of resection. Surveillance imaging was obtained at 3 months postoperatively and subsequently at yearly intervals.

Tissue Processing and Data Analysis

Tumor size and cavernous sinus invasion data were extracted from preoperative MR images. Tumors were categorized as microadenomas ($\leq$10 mm) or macroademonas ($>$10 mm) and cavernous sinus invasion measured according to the Knosp classification.[28]

GH-secreting pituitary adenomas were classified using morphological and immunohistochemical labels.[22] If most of the adenoma cells exhibited fibrous bodies on hematoxylin and eosin staining and a corresponding Golgi-pattern juxtanuclear spherical immunolabeling by cytokeratin CAM 5.2, adenomas were classified as sparsely granulated (SG). Adenomas were classified as densely granulated (DG) if a more uniform deeply acidophilic cytoplasm, more diffuse and strong GH labeling, and a perinuclear ring pattern of cytokeratin labeling were identified. Adenomas that exhibited two distinct cell types and/or both GH and patchy prolactin (PRL) immunolabeling were classified as mixed GH/PRL. Somatostatin receptor subtype 2A (SSTR2A) labeling was quantified using low-power light microscopy and identifying cytoplasmic or membrane labeling in adenoma cells. Tumors were classed as SSTR2A positive if at least 10% of adenoma cells stained for SSTR2A.[29]

Statistical analysis was undertaken using the MATLAB statistical toolbox (Natick, MA) including descriptive statistics, Kruskal-Wallis test, correlational analysis using analysis of variance with Bonferroni and Tamhane post hoc analysis to quantify the relationship between variables and binary logistic regression analysis to determine predictive values. Data are presented as plus or minus standard deviation with a p value < 0.05 considered significant.

Results

A total of 59 patients (41 women and 18 men) met the inclusion criteria (►**Table 1**), and ages ranged from 18 to 78 years (mean: 48.2 years). Overall, 6 of 59 patients (10.2%) reported visual field deficits. Diabetes insipidus (DI) was present preoperatively in two patients who had undergone previous pituitary surgery. Mean preoperative IGF-1 was 735 ± 371 ng/ml (range: 58–1755 ng/ml). Mean preoperative GH was 28 ± 49 ng/ml (range undetectable to 62.3 ng/mL). Macroadenomas were more common than microadenomas (48 versus 11), and among macroadenomas, the average maximum tumor diameter was 18.1 ± 9.9 mm. Most tumors were $\leq$30 mm in maximum diameter; however, eight were $\geq$30 mm; 20 macroadenomas were graded as Knosp 3 or 4, which indicated cavernous sinus invasion. Of the 11 patients with microadenomas, two had MR imaging data that was interpreted as showing no definitive adenoma. Tumor was

Table 1 Patient demographics and historical clinical characteristics ($n = 59$)

Demographic/characteristic	Number
Male, *n* (%)	18 (30.5)
Age, mean, y	48.2 (range: 18–78)
Knosp grade (%)	
0–2, *n*	39 (66.1)
3–4, *n*	20 (33.9)
Visual deficits at presentation, *n,* (%)	6 (10.2)
Diabetes insipidus at presentation, *n,* (%)	2 (3.4)
Microadenoma, *n,* (%)	11 (18.6)
Macroadenoma, *n,* (%)	48 (81.4); maximum diameter 18.1 ± 9.9 mm
Preoperative IGF-1, ng/mL mean ± SD	735 ± 371
Preoperative GH, ng/mL mean ± SD	28 ± 49

Abbreviations: GH, growth factor; IGF, insulinlike growth factor; SD, standard deviation.

identified during surgery and confirmed by pathologic analysis. Both patients achieved remission after resection.

Patients were followed for 13.4 ± 15.8 months. Complete biochemical remission was defined as random serum GH <1 µg/L or nadir GH after OGTT ≤0.4 µg/L. Overall, the remission rate was 52.5% after TSS. Mean age of patients in surgical remission (54.6 ± 13.2 years) was significantly higher than those patients not in remission (41.1 ± 15 years) ($p = 0.04$). Remission rates for micro- and macroadenomas were 81.8% and 45.8%, respectively. Patients who achieved remission had significantly smaller tumors compared with those who failed to attain remission (mean diameter 12.2 mm versus 23.4 mm) ($p < 0.000$). Using the Knosp classification system and preoperative MR images to determine cavernous sinus invasion, Knosp grade 0 to 2 tumors were associated with significantly higher rates of remission (74.4%) compared with Knosp grade 3 to 4 tumors (10%) ($p < 0.000$). In the two patients with Knosp grade 3 to 4 tumors who attained remission, residual tumor was visible on postoperative MR imaging. Based on the consensus criteria, the two Knosp grade 3 to 4 patients were still considered to be in biochemical remission. Patients who achieved remission had a significantly ($p = 0.001$) lower preoperative IGF-1 level (599.3 ± 297 ng/mL) compared with those who did not (912.4 ± 389.2 ng/mL) ($p = 0.001$). Preoperative GH levels were much lower for the patients who achieved remission (8.5 ± 8.1 ng/mL) than for those who did not (36.7 ± 31.6 ng/mL, $p < 0.000$).

There was no correlation between morphological subtypes, that is, DG, SG, mixed GH/PRL, and remission after TSS ($p = 0.67$), (►**Fig. 1**). Immunohistochemical SSRT2A data were available for 45 tumors. Seven tumor specimens (15.6%)

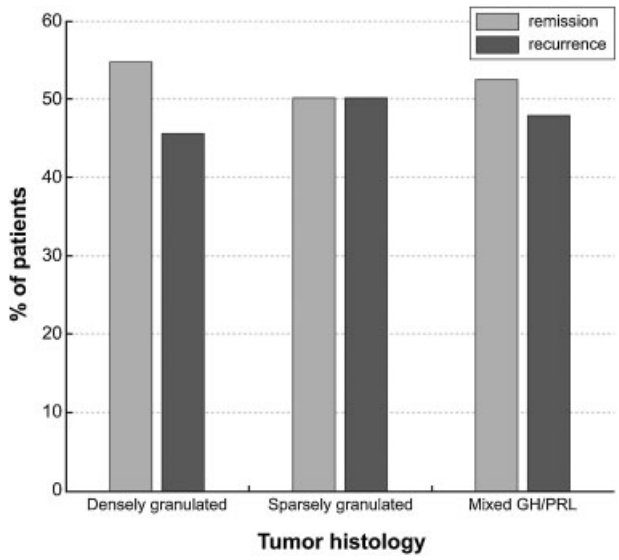

Fig. 1 Bar graph showing no histologic pattern, densely granulated, sparsely granulated, or mixed growth hormone/patchy prolactin (GH/PRL) was predictive of surgical remission ($p = 0.78$).

were SSRT2A negative; 38 (84.4%) were SSRT2A positive. SSRT2A immunohistochemical staining did not predict surgical remission (►**Fig. 2**). However, patients with SSRT2A-negative tumors had a significantly higher recurrence rate than those with SSRT2A-positive tumors, 57.4.3% versus 11.1% ($p = 0.003$) (►**Fig. 3**). The recurrence rate for patients with macroadenomas was 25%, and mean and median times to recurrence after surgery were 38 and 22 months, respectively.

Remission rate decreased significantly with repeat surgeries (►**Fig. 4**). After a first TSS, ~44.4% of patient reached

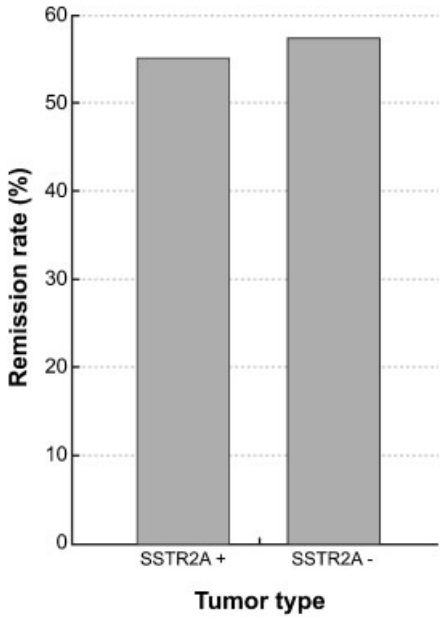

Fig. 2 Bar graph showing surgical remission rates were similar between somatostatin receptor subtype 2A (SSTR2A)-positive and SSTR2A-negative tumors (55.6% and 57.1%, respectively; $p = 0.933$).

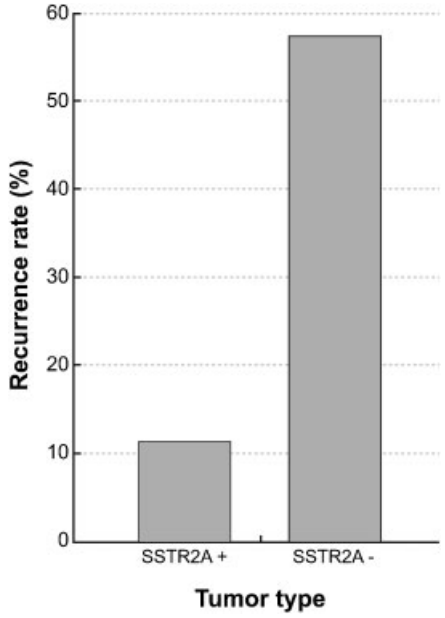

Fig. 3 Bar graph showing recurrence rate was lower for somatostatin receptor subtype 2A (SSTR2A)-positive than SSTR2A-negative tumors: 11% and 57%, respectively ($p = 0.003$).

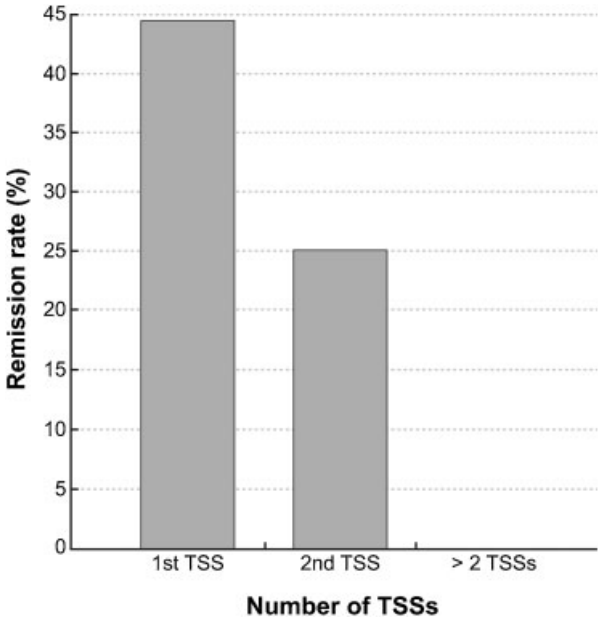

Fig. 4 Bar graph showing surgical remission rate decreased significantly with number of transsphenoidal surgery (TSS) ($p = 0.03$). After a first TSS, ~44% of patient went into remission; after a second TSS, only 25% reached remission.

remission, and of those patients who underwent a second surgery, only 25% reached remission. No patient who required more than two surgeries achieved remission.

There was a significant correlation between older age and greater likelihood of cure ($r = 0.432$; $p = 0.04$), whereas tumor size and Knosp scores were inversely correlated with surgical remission ($r = 0.518$; $p < 0.000$ and 0.238, $p < 0.000$, respectively). In addition, lower preoperative IGF-1 and GH levels were predictive of remission (►**Tables 2** and **3**).

Intraoperative cerebrospinal fluid (CSF) leaks were successfully managed with a short duration of CSF diversion with lumbar drain. No patient experienced CSF leak at discharge or subsequent follow up. At the 3-month follow-up, all six patients with a visual deficit before surgery reported improvement in vision. There were two patients with preoperative DI who continued to require medical treatment with desmopressin. Six patients (10.5%) experienced new postoperative DI, and two (3.5%) had symptoms that persisted beyond 3 months.

Discussion

Multiple reports of experience in treating GH adenomas using an endoscopic approach using the 2000 "Criteria for Cure of Acromegaly: A Consensus Statement"[18] have been published.[7,8,11,17,30–35] Two groups reported an overall acromegaly remission rate of 37% and 61%.[13,32] We report an overall remission rate of 52.5%. In our study, no patient experienced CSF leak at discharge or subsequent follow-up. A postoperative CSF leak rate of 0 to 4% via an endoscopic approach has previously been reported.[35] Our series confirms that, even under the most stringent remission criteria, microscopic TSS offers a remission rate for patients with acromegaly comparable with those of endoscopic approaches with a possible lower rate of CSF leak.

It has previously been reported that histologic and immunochemical characteristics such as granulation pattern are predictive of tumor response to medical therapies.[22–26] In a previous study, we reported that patients with DG tumors showed a significantly better response to medical treatment than those with SG or mixed GH/PRL tumors.[22] In this study, however, we showed that no histologic pattern was predictive of surgical remission. Similarly, patients with SSTR2A-positive tumors responded better (81%) to medical treatment, whereas those with SSTR2A-negative tumors exhibited no response.[22] Unlike histologic patterns, patients with tumors that were SSTR2A negative experienced a higher rate of recurrence (►**Fig. 3**). Among seven patients with a SSTR2A-negative tumor, four experienced recurrence. One patient who experienced recurrence achieved remission with a repeated surgery. In the other three patients, medical treatment after repeated surgery was required. It has been reported that SSTR2A negativity confers a significantly lower remission rate.[36] However, with a low number ($n = 7$) of SSTR2A-negative specimens, our series may have been underpowered to reach a similar conclusion. Overall, SSTR2A positivity confers a more favorable overall outcome. These results suggest that the SSTR2A marker predicts not only tumor responsiveness to medical therapy but also tumor growth pattern.

More than a third of tumors (20 of 59) were classified as Knosp grade 3 or 4, which indicates cavernous sinus invasion, in our study. These types of tumors continue to pose a challenge to remission postsurgery. The remission rate for this group of patients was 10%, and yet it accounted for >64% of patients who did not achieve remission. In two patients who did achieve remission, evidence of residual tumor was visible on postoperative MR images. Interestingly, in the

Table 2 Predictors of biochemical remission by univariate analysis ($n = 59$)

	Remission ($n = 31$)	Recurrence ($n = 28$)	p
Age, y	54.6 ± 13.2	41.1 ± 15.0	0.04
Male, *n* (%)	9 (29)	9 (32)	0.67
Microadenoma, *n* (%)	9 (81.8)	2 (18.2)	0.03
Macroadenoma, *n* (%)	22 (45.8)	26 (54.2)	0.78
Multiple surgeries, *n* (%)	2 (6.5)	10 (35.7)	<0.000
Maximum dimension, mm	12.2 ± 7.6	23.4 ± 10.2	<0.000
Knosp grade 3–4, *n* (%)	2 (6.5)	18 (64.3)	<0.000
Preoperative IGF-1 level, ng/mL mean ± SD	599.3 ± 297.0	912.4 ± 389.2	0.001
Preoperative GH levels, ng/mL mean ± SD	8.5 ± 8.1	36.7 ± 31.6	<0.000

Abbreviations: GH, growth factor; IGF, insulinlike growth factor; SD, standard deviation.

University of Virginia Health System experience, two patients with cavernous sinus invasion and Knosp grade 4 for whom the same stringent criteria was used were also in remission at the time of their evaluation.[13] Normalization of biochemical markers despite the presence of residual tumor was previously reported.[13,37]

In our study, we observed a trend that remission rate decreased significantly with repeated surgeries. Only 3 of 12 patients (25%) who underwent a second TSS achieved remission, and none of 4 patients who underwent more than two surgeries ever achieved remission. Although sample size is small and underpowered, it does raise the question of efficacy of a third TSS. In a recently published retrospective cohort study ($n = 14$) in patients who had undergone a second endoscopic TSS,[36] it was reported that after the second surgery, eight patients (57%) achieved remission. The authors concluded that repeated surgical intervention for acromegaly using endoscopic TSS offers similar surgical remission rates to initial surgical intervention. The only statistical significant predictor identified were preoperative GH levels before the second surgery. Given our study's small sample size and that of Wilson et al,[36] we believe future studies with larger cohorts are warranted. One goal of repeated surgeries is that surgical debulking will increase the likelihood of remission with medical therapy. Unfortunately, our study's sample size is not adequate to test this hypothesis.

In this first report on microscopic TSS outcomes defined using the 2000 criteria for cure of acromegaly consensus guidelines of GHr (fasting or nonfasting) of <1 mg/L and a GHn during an OGTT of <0.4 mg/L,[20] the overall cure rate was 52.5%.

Table 3 Predictors of biochemical remission by multivariate analysis

	r value	p value
Older age	0.432	0.04
Smaller tumor	−0.518	<0.000
Lower Knosp grade	−0.452	<0.000
Lower preoperative GH	−0.324	<0.000
Lower preoperative IGF-1	−0.235	<0.000

Abbreviations: GH, growth hormone; IGF, insulinlike growth factor.

Conclusions

For acromegaly patients treated with microscopic TSS and intraoperative MR imaging, we demonstrate that microscopic TSS continues to be efficacious. Remission rates for micro- and macroadenomas were 81.8% and 45.8%, respectively. Predictors of biochemical remission after surgery were older age, smaller tumor size, lower Knosp grade, and lower preoperative GH and IGF-1 levels. Remission rate decreased significantly with repeated surgery. Finally, patients with SSRT2A positively stained tumors were less likely to experience tumor recurrence and more likely to respond to medical treatment. Lower surgical remission rates and likelihood of biochemical recurrence among acromegalic patients with macroadenomas dictates that patients continue to be followed long term.

Acknowledgment

The authors thank Shirley McCartney, PhD, for editorial assistance.

Disclosures

Dr. Fleseriu has received consultant fees from Novartis Pharmaceuticals and Ipsen and is a principal investigator in clinical trials sponsored by Novartis Pharmaceuticals and Ipsen with research support to Oregon Health & Science University. Dr. Sun is in receipt of funds from the Congress of Neurological Surgeons Christopher C. Getch Flagship Fellowship Award. The remaining authors have nothing to disclose.

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